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# DIFFERENTIAL EFFECTS OF SPECIFIC ANTISERA ON THE REJECTION OF ALLOGENIC AND XENOGENIC SKIN GRAFTS BY SUBLETHALLY X-IRRADIATED MICE

by
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## ADMINISTRATIVE INFORMATION

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## ABSTRACT

Twelve to fourteen week old female $LAF_1$ mice, non-sensitized or pre-sensitized with two consecutive BALB/c or rat skin grafts, received 670 rad whole body X radiation and orthotopic tail grafts of $LAF_1$, BALB/c, C3D/2 and rat skin. Certain groups of mice received specific antisera intraperitoneally, produced in response to BALB/c or rat spleen cells or to two consecutive BALB/c or rat skin grafts. The data indicate that the first-set response to an allogenic skin graft can be significantly inhibited, in sublethally irradiated mice, by specific antisera, while the first-set response to a xenogenic skin graft remains resistant to similar treatment. Specific antisera had no effect upon a pre-existing second-set response. The significance of these data is discussed.

## SUMMARY


The Problem:

Under certain conditions, the immunological response of mice to foreign solid tissue grafts or to particular tumors can be inhibited by the administration of specific antisera produced in response to the same tissue or tumor. It is now generally accepted that at least one effector of this passively transferred "enhanced state" is circulating antibody. To date, attempts at "enhancing" the survival of normal solid tissue grafts have been confined primarily to grafts between certain strains of mice. The present communication deals with the effects of specific antisera upon allogenic (different strain of mouse) and xenogenic (different species) skin graft survival in non-sensitized and pre-sensitized sublethally irradiated mice.

The Findings:

The findings are described in the Abstract paragraph of this report.

## INTRODUCTION

The discovery of the phenomenon of "enhancement" of tumor growth, later shown to be passively transferred with serum from the pre-treated host (1-5), and its subsequent application to the transplantation of normal allogenic solid tissues (6-9), has provided the investigator with a potentially powerful tool for the "dissection" of the mammalian immune system. It is now generally accepted that at least one effector of the passively transferred "enhanced state" is circulating antibody, whether induced in response to lyophilized or viable tissue, neoplastic or normal (4,5).

It has been shown in mice (9) that high doses of specific antisera tend to prolong the survival of allogenic skin grafts, inhibit the development or expression of "homograft sensitivity" in response to certain antigenic stimuli, but have no effect upon a pre-existing second-set response. On the basis of their observations, Brent and Medawar (9) have postulated that "antiserum probably affects the process of sensitization itself, acting by a 'central' inhibition of unknown character rather than by obstructing the afferent or efferent pathways of response".

To date, attempts to promote the survival of homografts of normal tissues have been confined to allogenic grafts between certain strains of mice or other rodents. The present communication deals with the effects of specific antisera upon allogenic (H-2 difference) and xenogenic (rat) skin graft survival in non-sensitized and pre-sensitized,

sublethally irradiated (670 rad) mice.

Evidence will be presented demonstrating that the first-set response to an allogenic skin graft can be significantly inhibited, in sublethally irradiated mice, by passively transferred specific antisera, while the first-set response to a xenogenic skin graft remains resistant to similar treatment. Further, it will be shown that specific antisera, in the manner given, have no effect upon a pre-existing second-set response. The significance of these data will be discussed.

## MATERIALS AND METHODS

Twelve to 14 week old female (C57L x A)$F_1$, ($LAF_1$) mice were used as skin graft recipients. Skin graft donors were adult female $LAF_1$ (H2 ab), male BALB/c (H2 d) and (C3H x DBA/2)$F_1$, (C3D/2), (H2 Kd) mice, and 2-3 week old male and female Sprague-Dawley rats. The orthotopic tail skin grafting method of Bailey and Usoma was used (10). The details of grafting and the criterion of rejection (complete destruction of the engrafted tissue) have been reported previously (11). Mean survival time of the grafts and standard deviation (S.D.) are reported.

Non-sensitized $LAF_1$ mice received 670 rad whole body X radiation followed by 0.9-2.0 ml antiserum intraperitoneally, and were then grafted with $LAF_1$, BALB/c, C3D/2 and rat skin within six hours thereafter. Other mice were pre-sensitized with two consecutive BALB/c or rat skin grafts, and one week following the rejection of the second skin graft, they received 670 rad whole body X radiation, 1.0-1.1 ml antiserum

intraperitoneally, and were grafted as described above. The radiation factors (250 KVP, 15 ma; HVL 1.5 mm Cu; 30 rad/min) and details of exposure were the same as previously reported from this Laboratory (12).

The antisera were prepared in adult A/HeJ, C3H or $LAF_1$ mice of both sexes (see tables for particulars), either by means of three intraperitoneal injections, within nine days, of an homogenate of BALB/c or rat spleen cells (1/5 or 1/20 spleen respectively), or with two consecutive BALB/c or rat skin grafts. One week following the last injection of spleen cells or the rejection of the second skin graft, the mice were sacrificed, and the antisera were prepared from blood aspirated aseptically from the inferior vena cava. It was stored at -15°C until used. In one experiment, antisera were pooled from the three strains of mice which served as donors.

A previous communication (13) postulated the presence at the height of a vigorous second-set response of a non-specific agent which disrupts capillary integrity at the graft site, whether it be allogenic, xenogenic or isogenic. Therefore, "antiplasma" was prepared from blood aspirated into Heparin-wetted syringes (Heparin USP; 10 mg per ml), from adult A/HeJ mice which were at the height of rejection of their third consecutive BALB/c or rat skin graft. The"antiplasma" was administered immediately to the recipient mice (1.0-1.3 ml intraperitoneally).

It had been noted previously (11, 13) that non-irradiated and

sublethally irradiated (670 rad) mice, pre-sensitized with rat skin grafts, rejected subsequent first-set allogenic grafts significantly sooner than did their appropriate controls. It was postulated that this phenomenon represented a quantitatively expanded first-set response rather than a "non-specific" or "overflow" response to rejection of the rat skin graft (it was demonstrated previously that BALB/c or C3D/2 cells and rat skin share no common transplantation antigens with respect to $LAF_1$ mice (11)). Therefore, one group of mice pre-sensitized with rat skin grafts received 670 rad whole body X radiation, and all grafts except rat skin were placed. A second group, similarly pre-sensitized and irradiated, received 1.1 ml anti-BALB/c spleen serum intraperitoneally and all grafts were placed.

All mice were housed 10 per cage. The diet was Purina Lab Chow, and water containing 1% Neomycin was given ad lib.

RESULTS

First-Set Response Table I

All non-sensitized, sublethally irradiated $LAF_1$ mice given anti-BALB/c sera, produced in response to dissociated spleen cells or skin grafts, rejected subsequent BALB/c and C3D/2 skin grafts significantly later than did their appropriate controls (m.s.t. 29.7-40 days versus 21.1 days). Nine of 24 mice, so treated, rejected concurrent rat skin grafts somewhat later than did the control group (m.s.t. 27.2 days versus 22.7 days). However, only four of 15 mice given anti-rat sera

TABLE I

REJECTION OF ALLOGENIC AND XENOGENIC SKIN GRAFTS BY SUBLETHALLY IRRADIATED (670 RAD) $LAF_1$ MICE GIVEN ANTI-BALB/c OR ANTI-RAT SERA

| TYPE OF ANTISERUM | SOURCE | AMT ML | NO. MICE | ISOGRAFTS LOST | TIME FOR COMPLETE REJECTION MEAN SURVIVAL(DAYS) ± S.D. BALB/c | C3D/2 | RAT |
|---|---|---|---|---|---|---|---|
| None | | | 25 | 2 | 21.0 ± 3.5 | 21.1 ± 3.3 | 22.7 ± 3.5 |
| Anti-BALB/c spleen cells | A/HeJ | 2.0 | 2 | 0 | 40 | 32.5 | 26.5 |
| Anti-BALB/c spleen cells | A/HeJ | 1.0 | 8 | 1 | 29.1 ± 1.4 | 35.5 ± 12.2 | 27.2 ± 5.0 |
| Anti-BALB/c skin grafts | A,C3H,$LAF_1$* | 1.0 | 3 | 1 | 35.0 ± 1.4 | 34.0 ± 3.4 | 19.6 ± 4.4 |
| Anti-BALB/c skin grafts | A/HeJ | 1.0 | 10 | 0 | 29.9 ± 3.1 | 29.7 ± 3.1 | 22.0 ± 1.7 |
| Anti-BALB/c skin grafts | A/HeJ° | 1.0 | 1 | 0 | 30.0 | 30.0 | 30.0 |
| Anti-rat spleen cells | A/HeJ | 1.0 | 2 | 0 | 22.5 | 22.5 | 23.5 |
| Anti-rat spleen cells | $LAF_1$ | 0.9 | 4 | 0 | 24.2 ± 2.8 | 23.0 ± 3.4 | 24.0 ± 6.0 |
| Anti-rat skin grafts | A,C3H,$LAF_1$ | 1.0 | 5 | 1 | 18.0 ± 5.9 | | 22.0 ± 0.0 |
| Anti-rat skin grafts | A/HeJ° | 1.3 | 4 | 0 | 29.0 ± 8.0 | 25.0 ± 7.3 | 28.1 ± 5.6 |

*Pooled antisera

°Heparinized plasma collected at the height of rejection of the third consecutive skin graft and used immediately.

failed to reject rat skin grafts at the expected time (i.e., control: 22.7 ± 3.5 days). These mice had received anti-rat "plasma" and they also manifested a delay in rejection of concurrent allogenic skin grafts. All other mice receiving anti-rat sera rejected subsequent allogenic grafts at the expected time. At no time was there evidence either of an accelerated rejection of allogenic or xenogenic skin grafts or an increase in capillary fragility at the graft sites.

Second Set Response Table II

The second-set response of sublethally irradiated mice, pre-sensitized with BALB/c or rat skin grafts, was unaffected by antisera in the dosage given.

Sublethally irradiated mice, pre-sensitized with rat skin grafts, rejected subsequent allogenic skin grafts significantly sooner than did the control group despite the absence of a rat skin graft. However, when anti-BALB/c serum was given to a group of mice, similarly treated but receiving all grafts, the mean survival time of the allogenic skin grafts doubled (m.s.t. 31.6, 27.2 days versus 13.7, 14.3 days), i.e., allogenic skin graft survival was similar to that seen in the non-sensitized mice given anti-BALB/c sera, or as seen in sublethally irradiated mice previously sensitized with BALB/c spleen cells (13).

DISCUSSION

These and other data (9) clearly indicate that antisera, produced in response to normal allogenic tissues and in a manner which would be

TABLE II

REJECTION OF ALLOGENIC AND XENOGENIC SKIN GRAFTS BY SUBLETHALLY IRRADIATED (670 RAD) $LAF_1$ MICE PRE-SENSITIZED WITH BALB/c OR RAT SKIN GRAFTS AND GIVEN ANTI-BALB/c OR ANTI-RAT SERA

| MEANS OF SENSITIZATION | TYPE OF ANTISERUM | AMT. ML. | NO. MICE | ISOGRAFTS LOST | TIME FOR COMPLETE REJECTION MEAN SURVIVAL(days) ± S.D. BALB/c | C3D/2 | RAT |
|---|---|---|---|---|---|---|---|
| BALB/c skin grafts | anti-BALB/c spleen | 1.0 | 7 | 2 | 11.1 ± 1.8 | 11.5 ± 1.0 | 20.2 ± 1.7 |
| Rat skin grafts | anti-rat spleen | 1.0 | 7 | 2 | 18.8 ± 8.7° | 16.0 ± 9.1* | 4.3 ± 0.6 |
| Rat skin grafts# | none | | 7 | 0 | 13.7 ± 3.8 | 14.3 ± 2.3 | none |
| Rat skin grafts | anti-BALB/c spleen | 1.1 | 9 | 0 | 31.6 ± 6.0 | 27.2 ± 3.8 | 5.7 ± 1.3 |

° 1/7 BALB/c skin grafts rejected at 8 days.

* 3/7 C3D/2 skin grafts rejected between 6-8 days.

# These mice were not grafted with rat skin after irradiation.

expected to induce a state of "sensitivity" in the host, are capable of significant inhibition of the first-set response to subsequent allogenic skin grafts. However, the second-set phenomenon appears to be resistant to the action of the same antisera. These observations tend to support the hypothesis of "central inhibition" as the means by which specific antisera induce the "enhanced state".

However, neither the first nor the second-set response to a xenogenic skin graft appears to be affected by the presence of relatively large amounts of specific antisera. These and other data (11, 13) argue most strongly for the existence within the "immune system" of functionally distinct cell lines or systems, i.e., xenogenic solid tissue grafts provoke a response from a "cell line" functionally and perhaps phylogenetically different from that "cell line" which would respond to an allogenic skin graft. Rat skin does possess, in addition, other antigens which stimulate cell lines capable of reacting to allogenic skin grafts. This was demonstrated when the accelerated rejection of allogenic skin grafts by sublethally irradiated mice previously sensitized with rat skin grafts was abrogated by means of a specific antiserum (anti-BALB/c). This phenomenon most likely represents a quantitatively expanded, "radioresistant" first-set response.

A previous communication (13) has suggested the uniqueness of the "sensitivity" evoked by skin grafts, allogenic or xenogenic, as opposed to that induced by other means (see also 9, 14). It was demonstrated that the "homograft sensitivity" elicited by skin grafts was markedly

more radioresistant than was that produced with dissociated cells. Further, sensitization with allogenic dissociated spleen cells resulted in a prolongation of survival of subsequent allogenic skin grafts in sublethally irradiated mice when compared to the appropriate controls, i.e., "self enhancement".

On the basis of the cited data, it is suggested that the second-set response is indeed unique. It is postulated that the second-set response to an allogenic skin graft represents the immunological response of a minimum of two cell types or systems: first, a "monitor cell" (perhaps thymic in origin) responds to the incoming antigenic stimulus, bears prime responsibility for humoral antibody production either directly or through collateral cells, and is responsive to circulating antibody levels, i.e., positive feed-back mechanism; and second, an "effector cell" is activated and "armed" by the "monitor cell". The latter cell line or system remains "armed" and accounts for the persistence of the second-set response. Similarly, the second-set response to a xenogenic skin graft may represent a two stage response contained within a primigenial cell line or system, or perhaps, be the manifestation of two separate biochemical steps within a single cell. It is realized that the above is most speculative and that even if it represented a first approximation to the existing nature of things, many ancillary steps and auxiliary cell systems (macrophages, polymorphonuclear cells, etc.) involved in the rejection of a skin graft

have been neglected for the purposes of this discussion.

However, within this hypothetical frame-work "enhancement" of graft survival would be the resultant of prior stimulation of the "monitor cell" without concomitant "arming" of the "effector cell"; that is, the stimulus would be such as to call forth the production of humoral antibodies exclusively, and the "monitor cells" being sensitive to the level of antibody would fail to respond appropriately to a second stimulus in the form of a homograft. Passive enhancement would similarly be explained. Further, the "sensitivity," evoked by dissociated cells appears to represent an expansion within the "line of monitor cells"; the accelerated rejection of subsequent skin grafts is a manifestation of this <u>quantitative</u> change.

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2. Skin.
3. Transplantation.
4. Radiation tolerance.
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received 670 rad whole body X radiation and orthotopic tail grafts of $LAF_1$, BALB/c, C3D/2 and rat skin. Certain groups of mice received specific antisera intraperitoneally, produced in response to BALB/c or rat spleen cells or to two consecutive BALB/c or rat skin grafts. The data indicate that the first-set response to an allogenic skin graft can be significantly inhibited, in sublethally irradiated mice, by specific antisera, while the first-set response to a xenogenic skin graft remains resistant to similar treatment. Specific antisera had no effect upon a pre-existing second-set response. The significance of these data is discussed.

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